

REMARKS

Claims 1-30 were pending in the application. In this Office Action the Examiner has withdrawn claims 1-22, 25 and 27 from consideration as being drawn to a non-elected invention. Claims 25 and 27 have apparently been withdrawn as being drawn to a non-elected species of Group III. Claims 23, 24, 26 and 28-30 have been examined. By this amendment claims 23, 24, 28, and 29 have been amended to more clearly and precisely set forth the present invention. The amended claims are fully supported by the specification as filed as set forth in detail below, therefore no new matter has been added.

The disclosure has been objected to for certain informalities. In particular, the Examiner has noted that the sequence identifiers have not been included after the peptide sequences LLHETDSAV and ALFDIESKV at pages 7 and 8. As set forth above the specification has been amended to insert the proper sequence identifiers where necessary. Also, The Examiner has noted that on page 7 the recitation of Figures 9A-C is not consistent with the labeling of the figure filed in the application. Applicants note that Figure 9 was filed as an informal drawing and contains three panels which have not been separately designated. Correction will be made by submission of formal drawings upon an indication of allowable subject matter.

Rejections Under 35 USC § 112:

Claims 23, 24, 26 and 28-30 stand rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner believes that claim 23 is indefinite in the recitation of "exposed" to antigen because the metes and bounds of the actions encompassed by the term "exposed" cannot be determined. The Examiner has suggested that one way to clarify the term is to include that the exposure results in presentation of the antigen or in dendritic cells which have taken up antigen.

While Applicants believe that claim 23 is definite as originally presented, in order to further expedite prosecution of the present application claim 23 has been amended to recite "wherein said human dendritic cells take up and present said antigen." This amendment is believed to obviate the Examiner's rejection.

Further, claims 24 and 30 are believed to be indefinite in the recitation of "the cancer patient," the Examiner indicating a lack of antecedent basis. Applicants believe that the Examiner intended to include claims 24 and 30 in this rejection and have amended these claims to recite that the cancer cells have been isolated "from a cancer patient." The present amendment is believed to obviate the Examiner's rejection of claims 24 and 29 under 35 USC § 112, second paragraph.

Applicants respectfully request the Examiner to the reconsider and withdraw the rejections of claims 23, 24, 26, and 28-30 under 35 USC § 112, second paragraph, in light of the above amendments to the claims and associated remarks.

Claims 23, 24, 26, and 28-30 stand rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner believes that the claims pending in the application now recite limitations which were not clearly disclosed in the specification, as filed, and now change the scope of the disclosure. The limitations now recited in the claims which the Examiner appears to believe were not clearly disclosed, the Examiner also believes introduce new concepts and violate the description requirement of the first paragraph of 35 USC § 112. In particular, the Examiner appears to believe that the specification, as filed, only contemplated dendritic cells which present prostate cancer antigens and that the disclosure did not contemplate dendritic cells which present normal prostate antigens from normal prostate tissue as now encompassed by the claim language.

Applicants traverse this basis for rejection as set forth below, but also have amended claim 23 to clarify the present invention. Claim 23 has been amended to recite "[a] composition comprising: isolated human dendritic cells which have been exposed, *in vitro*, to a prostate antigen." Support for this amendment is found in the specification as filed at, for example, page 8, the third through seventh lines from the bottom of the page, wherein dendritic cells obtained from human donors "once exposed to a prostate cancer antigen or specific antigenic peptides are administered to a prostate cancer patient"(emphasis added). Further, at

page 9, lines 1-4 the specification recites "the description of the invention is divided into the following sections: . . . (2) prostate specific antigens for presentation by DC's." Further, within Section 5.2 various examples of both prostate specific antigens and prostate cancer antigens for presentation by dendritic cells are specifically set forth.

In particular, at page 13, lines 17-18 the antigen provided is a prostate tumor cell lysate of LNCaP, a prostate cancer cell line. At page, 13, lines 24-25 the antigen provided is a prostate tumor cell lysate recovered from surgical specimens (including the patient to be treated, see page 13, lines 25-28). Further, the antigen presented by dendritic cells is set forth to be a membrane preparation of tumor cells of a prostate cancer patient. A prostate antigen which is found in both normal and cancer tissue is specifically provided in the specification at page 13, lines 29-31, wherein purified prostate specific membrane antigen (PSMA, also known as CYPB antigen and as PSM antigen) which specifically reacts with monoclonal antibody 7E11-C5 is disclosed. PSMA is known in the art as a membrane associated antigen of human normal prostatic epithelium and human prostatic cancer epithelium (US Patent 5,162,504 (AB)). At page 14, line 6 through the end of page 15 of the specification as filed various peptides from within PSMA are specifically set forth as antigens which can be presented by dendritic cells which are encompassed by the present invention.

Still further, the specification provides another normal prostate antigen, designated prostate specific antigen (PSA), for presentation by dendritic cells. PSA is produced exclusively in males by the columnar epithelial cells of the prostate, and periurethral glands. Normal prostate epithelial cells and benign hyperplastic tissue actually produce more PSA protein than malignant prostate tissue. PSA is not a traditional tumor marker, in that, it is not produced in higher quantities by tumor cells, but rather abnormalities in the prostate gland architecture resulting from trauma or disease can lead to increased "leakage" of the protein into the stroma and then into the bloodstream (see, last paragraph on page 731 bridging to page 731 of McCormack et al. *Urology* 45:729-744 (1995); reference CB, Form 1449, Information Disclosure Statement filed December 1, 1998.

The specification, as filed, also discloses the use of prostate mucin antigen as recognized by monoclonal antibody PD41 for presentation by dendritic cells (see, the

specification as filed at the fourth line from the bottom of page 16 through page 17, line 2).
This particular mucin antigen is specific to prostate tumor cells.

Applicants note that patent application serial number 08/509,254, filed July 31, 1995 (issued as US Patent 5,788,963, August 4, 1998 (AF)), the parent to the instant application, also disclosed the use of LNCaP lysate, patient tumor lysate, patient tumor membrane preparation, PMSA, peptides of PMSA, PSA, peptides of PSA, and PMA as antigens for presentation by dendritic cells. See, for example pages 12 through 14 of the application as filed (column 8, line 38 through column 9, line 24).

Therefore, contrary to the opinion of the Examiner, Applicants not only contemplated the use of prostate tumor antigens for presentation by dendritic cells but also contemplated and actually reduced to practice the use of prostate antigens from both tissues and cells which would be considered normal and cancerous for presentation by dendritic cells. Contemplation of the uses of both normal and cancer associated tumor cells dates back to, at least, July 31, 1995, the filing date of the parent to the present application. Applicants assert that no new matter has been added to the application and that the pending claims are fully described and enabled by the specification as filed. It is respectfully requested that the Examiner reconsider and withdraw the rejection under 35 USC § 112, first paragraph, of claims 23, 24, 26, and 28-30.

Rejections Under 35 USC § 102:

Claims 23 and 24 stand rejected under 35 USC § 102(e) as allegedly anticipated by Cohen et al. In particular, the Examiner believes that Cohen et al. teach isolated dendritic cells which have been exposed to prostate tumor lysate. Applicants traverse this ground for rejection. It is well settled for anticipation, each and every limitation of a claimed invention must be disclosed in a single prior art reference (*In re Spanda*, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990)). In addition, the reference must be enabling and describe the applicants claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the art.

Cohen disclose the isolation of blood cell fractions from individuals by leukopheresis. The fractions designated 150, 160, 170, 180, and 190 were pooled and one half of the sample was subjected to calcium ionophore treatment. Each cell population was also

incubated in the presence of an autologous tumor cell lysate or in the presence of keyhole limpet hemocyanin. The various cell populations were then tested for the presence of certain cell surface markers that have been used to characterize monocytes (CD3, CD14, CD20 and CD56) and dendritic cells (DR, B7.1(CD80) and B7.2(CD86)). Cohen characterizes the isolated cells in the normal donor which were not treated with calcium ionophore as comprising a "vast majority of cells . . . remained CD14⁺ indicating that they remained monocytes" and "a subset of the cocktail negative (dendritic) cells showed marked upregulation of HLA-DR, B7.1 and B7.2." Further, Cohen characterizes the vast majority of cells from the normal donor which were treated with calcium ionophore as being found to be cocktail negative and markedly upregulated for HLA-DR, B7.1 and B7.2. No disclosure is provided in Cohen which demonstrates that the cells, which phenotypically as characterized by cell surface markers, had apparently converted to dendritic cells were functional in any way, much less whether the cells characterized as dendritic processed and presented antigen from KLH. Further, no negative controls are provided for the normal donor which were not antigen stimulated for comparison of the cell surface phenotype.

Cohen also examined monocyte cell fractions isolated from colon cancer patients. The vast majority of cells isolated from the cancer patient which were not treated with calcium ionophore remained CD14⁺ while a subset of CD14⁺ negative cells showed a "modest" upregulation of HLA-DR, and B7.2, but only a "little upregulation" of B7.1. The majority of cells isolated from the colon cancer patient which were treated with calcium ionophore were converted to cocktail negative indicating that they "had become dendritic cells," and similar to the cocktail negative cells which had not been treated with ionophore, there was a marked upregulation of HLA-DR and B7.2, but a less uniform upregulation of B7.1.

As with the monocytes isolated from a normal donor, no data is provided which demonstrates that the cells induced to express markers associated with dendritic cells are actually functionally antigen presenting cells. The markers used by Cohen and others, i.e., CD14, B7.1 and B7.2, may be useful to demonstrate that monocytes have, at least phenotypically (based on the expression of cell surface markers) differentiated to a dendritic phenotype, but provide no evidence of differentiation of the monocytes to a functional

dendritic cell phenotype as would be demonstrated by antigen processing and presentation. Therefore, based on the disclosure of Cohen, the skilled artisan could not have anticipated nor had a reasonable expectation that *in vitro* exposure of monocytes to a calcium ionophore followed by exposure to a prostate antigen would provide a cell population which was phenotypically defined as comprising a dendritic cell composition wherein the dendritic cells could take up and present a prostate antigen.

Further, Cohen et al. describe at column 12, line 15 through column 13, line 27 a prophetic example describing a treatment of cancer in a patient with cells isolated from the patient treated with ionophore and converted to a dendritic cell phenotype, as defined by the expression of CD14, B7.1 and B7.2, which have been incubated in the presence of a prostate tumor lysate. Applicants do not believe that one of skill in the relevant art could anticipate the claims of the present invention. As above, there is no disclosure or suggestion that the cells treated with calcium ionophore and exposed with tumor cell lysate could process and present antigen as required to anticipate a limitation of the pending claims.

As an indication of the state of the art prior to the filing of the present application, Applicants provide attached hereto an article by Pickl et al. (*J. Immunol.* 157:3850-3858 (1996)). Pickl et al. describe the presence of certain cell surface markers on isolated monocytes and monocytes which have been treated with a combination of either GM-CSF and IL-4 or GM-CSF and TNF α . Among the markers measured were CD14, CD80 (B7.1) and CD86 (B7.2). In addition the cells were also examined for their functional ability to initiate T cell responses and for their efficiency to present antigen (tetanus toxin). The authors conclude:

. . . monocyte-derived cells are . . . extremely efficient in presenting soluble Ag to autologous T cells and dramatically differ also in that respect from freshly isolated GM-CSF plus TNF- α -cultured monocytes, which require 100- to 1000-fold higher AG concentrations for induction of similar T cell proliferation indices. The observed functional discrepancy between GM-CSF plus IL-4-treated cells and GM-CSF plus TNF α -cultured monocytes is particularly striking given the not

quite absolute, but quite remarkable similarities of the surface marker profiles of these two cell types.

(Page 3857, right column, paragraph 5).

Applicant suggests that at the date of filing the present invention a skilled artisan could not conclude, based only on the analysis of cell surface markers CD14, B7.1 and B7.2, monocytes stimulated with an ionophore were functional dendritic cells. Cohen et al., although they expose cells which have been identified as dendritic cells based on the presence of certain cell surface markers, they do not disclose data which could anticipate that the cells would be active dendritic cells capable of processing and presenting antigen. It can not be assumed that the presentation of cell surface antigens unassociated with dendritic cell antigen presentation activity can be extrapolated to the human dendritic cells of the presently claimed invention.

Applicants respectfully request the Examiner to reconsider and withdraw the rejection of Claims 23 and 24 under 35 USC § 102(e) as anticipated by Cohen et al. in light of the above remarks.

Claims 23 and 24 stand rejected under 35 USC § 102(a) as allegedly anticipated by Tjoa et al. In particular, the Examiner believes that Tjoa et al. teach compositions isolated from dendritic cells exposed to LNCaP lysate. Applicants traverse this rejection because Tjoa et al. is not a proper reference under 35 USC § 102(a).

Applicants respectfully direct the Examiner attention to the August 1995 publication date of Tjoa et al., Prostate 27:63-69. The present application is a continuation under 37 CFR 1.53 of PCT US96/12389, filed July 31, 1996, which in turn is a continuation-in-part of application serial number 08/509,254, filed July 31, 1995 the filing date of which is prior to the publication date of Tjoa et al. Claims 23 and 24, as above are fully disclosed and enabled by the grandparent application 08/509,254. For example, LNCaP lysate is representative of a prostate cancer cell antigen while, prostate specific antigen and prostate membrane specific antigen can be found in both normal and cancerous prostate cells.

As Tjoa et al. was published after the filing date of the priority application which supports and enables claims 23 and 24, Applicants respectfully request the Examiner to

reconsider and withdraw the rejection of claims 23 and 24 over Tjoa et al. under 35 USC § 102(a).

Rejections Under 35 USC § 103

Claim 26 stands rejected under 35 USC § 103(a) as allegedly unpatentable over Cohen et al. or Tjoa et al, as applied to claims 23 and 24 in view of Lutz et al. In particular, the Examiner believes that Cohen et al. disclose isolated dendritic cells which have been exposed to prostate tumor lysate and Tjoa et al. disclose compositions isolated from dendritic cells exposed to LNCaP lysate, but that neither teach extended life span dendritic cells. Lutz et al. the Examiner believes teach making immortalized dendritic cells and further teach that the problem of being unable to maintain dendritic cells *in vitro* for long periods of time can be overcome by immortalizing them. Therefore, it is the Examiner's opinion it would have been *prima facie* obvious of one of ordinary skill in the art at the time of the invention to substitute the dendritic cells of Cohen et al. or Tjoa et al. with the immortalized, extended life span, cells of Lutz et al.

Applicants respectfully disagree and traverse this rejection.. As above, Cohen et al. teach the "activation" of isolated cell fractions from peripheral blood with a calcium ionophore to phenotypically, as measured by the upregulation of certain cell surface makers, resemble dendritic cells. There is no evidence that the "activated" cells are functionally dendritic cells capable of processing and presenting antigen. One of skill in the art would be unable to reasonably conclude that the methods described by Cohen et al. resulted in the dendritic cells which have processed and present prostate antigen as currently claimed. Further, Tjoa et al. published after the filing date of the grandparent application of the instant application removing the reference as prior art for consideration under 35 USC § 103.

Lutz et al. is a standard reference that teaches immortalizing dendritic cells. In light of the discussion above with respect to Cohen et al. and Tjoa et al., it would have been non-obvious to expose dendritic cells to a prostate antigen, including but not limited to PSMA, for antigen processing and subsequent presentation to T cells. Lutz et al. add nothing to make it obvious to provide modified dendritic cells, i.e., extended life span or immortalized dendritic cells, which have processed such antigens. Furthermore, extended life span dendritic cells of

claim 26, unlike the immortalized dendritic cells disclosed in Lutz et al., are limited in the number of replicative cycles they may undergo. It would not have been obvious to one of ordinary skill in the art, in view of Cohen et al. or Tjoa et al., and Lutz et al., to make or use extended life span dendritic cells which process and present prostate antigen as presently claimed. Thus, Applicants respectfully submit the Examiner has failed to make a *prima facie* case of obviousness. Applicants respectfully request the Examiner reconsider and withdraw the present rejection.

Claims 28 and 29 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Cohen et al or Tjoa et al. as applied to claims 23 and 24 in view of Taylor et al. The Examiner believes Cohen and Tjoa teach as set forth above, and that Taylor et al teach cryopreservation of dendritic cells and that the cryopreserved dendritic cells can be used in immunological procedures. It is the Examiner's opinion that it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to substitute the dendritic cells of Cohen or Tjoa with the cryopreserved dendritic cells of Taylor et al. with a reasonable expectation of success one that one would have been motivated to do so in order to preserve the previously isolated dendritic cells.

Applicants respectfully disagree and traverse the rejection. Taylor is a standard reference that teaches cryopreservation of dendritic cells. In light of the discussion above with respect to Cohen et al. and Tjoa et al. as references in the rejection of claims 23 and 24, it would have been non-obvious to make compositions of dendritic cells which have been exposed *in vitro* to prostate antigen, wherein said dendritic cells take up and present said antigen, including but not limited to PSMA, for subsequent presentation to T cells. Taylor et al. adds nothing to make it obvious to provide a composition of dendritic cells as presently claimed. As discussed above, with respect to claims 23 and 24, the references fail to provide motivation for one of ordinary skill in the art to combine the references.

Even should the references be combined, i.e., Cohen et al. and Taylor et al., the composition disclosed by Cohen et al. and cryopreserved by the methods of Taylor et al. would necessarily have resulted in the claimed composition. Specifically, there is not teaching that the composition obtained by the combination of references would have provided dendritic cells which were cryopreserved would remain capable of demonstrating even the dendritic cell

phenotype described by Cohen et al. much less remain capable of processing and presenting prostate antigen for subsequent presentation to T cells. Thus, for the same reasons, the Examiner has failed to make out a *prima facie* case of obviousness. Therefore, Applicants respectfully request the Examiner to reconsider and withdraw the present rejection.

Claim 30 stands rejected under 35 USC § 103(a) as allegedly unpatentable over Cohen et al. or Tjoa et al, as applied to claims 23 and 24 in view of Taylor et al. as set forth for claims 28 and 29 further in view of Lutz et al. In particular, the Examiner has reiterated the teachings of Cohen et al., Tjoa et al., and Taylor et al., and further believes that Lutz et al. teach making immortalized dendritic cells and also teach that the problem of being unable to maintain dendritic cell *in vitro* for long periods of time can be overcome by immortalizing them. It is therefore the Examiner's opinion it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the present invention to substitute the dendritic cells of Cohen et al. or Tjoa et al., as modified by Taylor et al. with cryopreserved, immortalized, extended life span cells of Lutz et al. with a reasonable expectation of success.

Applicants respectfully must disagree and traverse this rejection. In light of the discussion above with respect to claims 23, 24, 28 and 29, it would have been non-obvious to provide a composition of dendritic cells exposed *in vitro* to a prostate antigen, including but not limited to PSMA, for processing and subsequent presentation to T cells. As the dendritic cell composition itself is non-obvious, Lutz et al. adds nothing to make it obvious to immortalize dendritic cells that have been previously cryopreserved. Further, as discussed above in regard to claims 23, 24, 28 and 29, the references provide no motivation for one of ordinary skill in the art to combine the various references cited. Thus, for the same reasons, the Examiner has failed to make out a *prima facie* case of obviousness. Applicants therefore respectfully request the Examiner to reconsider and withdraw this rejection of claim 30.

CONCLUSION

In view of the foregoing, Applicants believe all objections and rejection of the Application and claims have been addressed and that the claims now pending in this

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Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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